REMARKS

Status of the Claims

Claims 1-3 and 5-24 are pending in the application, claim 4 having been previously canceled.

35 U.S.C. § 112, second paragraph

Claim 23 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention (Office Action, page 2). Specifically, the Examiner states that the preamble in claim 23 lacks correspondence to the claim steps. As amended herein, the claim steps in the body of claim 23 now corresponds to the preamble. In view of this amendment, applicant respectfully requests withdrawal of this rejection and reconsideration of the rejected claim.

35 U.S.C. § 103(a)

Claims 1-3, 5-22, and 24 have been rejected as being unpatentable over U.S. Pat. No. 5,631,165 ("Chupp") in view of U.S. Pat. No. 5,200,323 ("Chang"), U.S. Pat. No. 6,228,652 ("Rodriguez") and Patent Application WO 98/39634 ("Samsoondar"). The applicant respectfully traverses this rejection for the reasons discussed below.

Briefly, Applicant's invention relates generally to new methods for correcting interference to hematology and clinical chemistry parameters. The interference can occur during the analysis of whole blood, plasma and serum samples due to the presence of cell-free blood substitutes which are added to a patients blood as supplementary oxygen carriers. The present invention provides an automated method to correct clinical chemistry results and hematology

blood parameter results and values, e.g., mean cell hemoglobin (MCH) and mean cell hemoglobin concentration (MCHC) to account for interference error. Suitable instruments for carrying out the analyses of the present invention possess two analytic channels which measure the concentration of hemoglobin in a blood sample.

The applicant has amended independent claims 1, 9, 15 and 16 to more clearly point out that the present invention measures intracellular and total hemoglobin without requiring prior separation of the sample into it's cellular and plasma components. In light of these amendments the rejection under § 103 is traversed.

The Examiner has rejected claims 1-3, 5-22 and 24 under 35 U.S.C. § 103 based on the combination of four references. As discussed below, none of the four references teach or suggest the present invention, alone or in combination. Further there is no motivation to combine these references in the manner suggested by the Examiner.

Chupp

Chupp relates generally to the analysis of whole blood samples using a "conventional hematology analyzer integrated with a fluorescence cytometery analyzer" (Abstract). In the method disclosed in Chupp, hemoglobin is measured after the red blood cells are lysed. Chupp teaches the mathematical formulas for MCH and MCHC (column 54 lines 21-3). There is no teaching of the use of blood substitutes containing extracellular hemoglobin, the measurement of hemoglobin on a cell-by-cell basis, or the use of a subtraction step in the correction of the hematology values. In particular, there is no teaching of measureing intracellular hemoglobin in the presence of an exogeneous heme-colored blood substitute extracellular to the red blood cells.

Chang

Chang discloses a method of testing blood substitutes for safety before they are given to human patients. In Chang, a whole blood sample is taken from the patient and the red cells removed to make a plasma sample. The blood substitute is then added to the plasma sample to test if complement is activated (Abstract). It is important to note that the blood substitute is added to human plasma, which lacks cellular hemoglobin because the red cells have been removed. Chang does not disclose methods of measuring the concentration of either intercellular or extracellular hemoglobin or how to correct hematology values based on the presence of blood substitutes in a sample. Applicant fails to see how Chang has any relevance to the pending claims.

Rodriguez

Rodriguez discloses a blood analyzing instrument for measuring "the DC volume, RF conductivity, light scattering and fluorescent characteristics of blood cells" (Abstract). The analyzer produces a report on the "cellular hemoglobin information for red blood cells and reticulocytes, mean volumes of the aforementioned cell types and derived parameters including total hemoglobin for the sample" (column 13, lines 30-33). The disclosed analyzer can also measure "erythrocyte cell-by-cell hemoglobin" (column 13, line 38). Rodriguez does not disclose measurine the level of a blood substitute in a sample containing red blood cells or how to correct hematology values for the presence of a heme-colored blood substitute.

Samsoondar

Samsoondar discloses a method "whereby the concentration of a blood substitute, such as cross-linked hemoglobin, in a serum or plasma specimen is rapidly and accurately identified and quantified" (emphasis added) (Abstract). Further, the method takes "the measured concentration

of the blood substitute and uses it to correct for its effect, if any, on a measured analyte concentration e.g. serum/plasma total protein." However, Samsoondar does not teach or suggest cell-by-cell measurement of hemoglobin in the presence of extracellular blood substitutes as recited in the pending claims. Rather, Samsoondar actually teaches away from the present invention by requiring separation of red blood cells from serum or plasma prior to the measurement of hemoglobin (emphasis added).

Because none of the cited references teach or suggest the measurement of intracellular hemoglobin in the presence of an extracellular blood substitute, the rejection is improper. Further, there is no motivation to combine Chupp, Chang, Rodriguez and Samsoondar as discussed below.

As stated in MPEP 2143.01, "Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *See In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

The Examiner states that "one of ordinary skill in the art would have been motivated to enhance the automated hematology analyzer and method for correcting MCH and MCHC values in blood, as stated by Chupp et al., by including all types of blood samples in use at the time of the invention such as those containing modified hemoglobin blood substitutes, as stated by Chang et al." As an initial matter, we note that there is no suggestion whatsoever to make the suggested modification. That is, Chupp is silent with respect to extracellular blood substitutes

and Chang does not even relate to measureing concentrations of any analyte. Applicant respectfully submits that the Examiner's conclusory suggestion of a motivation to combine Chupp and Chang is improper. *See Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993); MPEP 2143.01. Chang merely teaches the availability of blood substitutes but does not teach or suggest the problem solved by the present invention, that is the presence of blood substitutes in blood samples causing interference with hematology measurements. The Examiner has not pointed to any objective rationale that would suggest that the blood substitutes of Chang could be measured in the presence of red blood cells containing hemoglobin using the method and apparatus of Chupp.

The Examiner specifically cites Chang (col. 4, lines 11-30) as a motivation to combine the cited references. Lines 11-15 of Chang read "it would be highly desirable to be provided with an *in vitro* screening test which would be based on using human blood or plasma to determine the safety of modified hemoglobin blood substitutes for human prior to clinical use."(emphasis added). Applicant fails to see how a statement relating to the "safety" of a blood substitute in any way suggests measuring the blood concentration of a blood substitute or the concentration of cellular hemoglobin in the presence of that substitute. Chang does not disclose or suggest any methods for measuring exogeneous blood substitute levels in patients who have received them, let alone measureing such levels in the presence of blood substitutes in blood samples. Because Chang does not disclose measuring the levels of any blood component whatsoever there is no motivation to combine Chang with any of the cited references.

It is well established that "if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious." *In re*

Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). For this reason, there is insufficient motivation to combine Chupp with any of the cited references. That is the skilled artisan would understand that lysing red blood cells according to the method of Chupp precludes discrimination between intracellular and extracellular hemoglobin as required by the present invention. Further, if the red blood cells are lysed according to Chupp one cannot measure intracellular hemoglobin on a cell-by-cell basis as also required by the claims. For at least this reason it is inappropriate to combine Rodriguez with Chupp.

Similarly, in order to practice the invention of Samsoondar, it is necessary to first remove the red cells so that one has a serum or plasma sample. In contrast, Rodriguez is directed to the "measurement of erythrocyte cell-by-cell hemoglobin" (column 13, line 38). Because Samsoondar teaches the removal of the red cells that are measured by Rodriguez, the combination of Samsoondar and Rodriguez would be inoperative. That is, the method of Rodriguez requires a cellular substrate where as Samsoondar removes the cellular material. This combination clearly would not be suitable for measuring the presently claimed analytes on a cell-by-cell basis without a prior separation step, as now required by the claims.

Similarly, Chupp measures hemoglobin by lysing the red cells in a sample of whole blood (column 53, line 65 to column 54, line 7). If one were to combine Samsoondar with Chupp, the teachings of Samsoondar would have the skilled artisan remove the red blood cells. This would defeat the purpose of Chupp because there would be no hemoglobin to be measured. Thus the combination of Chupp and Samsoondar would also be inoperable.

Applicant asserts that the Examiner has failed to establish a *prima facie* case of obviousness under 35 U.S.C. § 103 for at least the foregong reasons.

On page 7 of the Office Action the Examiner states that the specification does not have a clear and concise definition of "cellular hemoglobin." And proposes to define the term cellular hemoglobin as "hemoglobin from a cell." Applicant is confused by this assertion because the meaning of the term is abundantly clear to the skilled artisan based on the teachings of the application. Specifically, paragraph 42 ". . . the intracellular (or cellular) hemoglobin (i.e. Calculated HGB) and extracellular HGB (i.e. HGB Delta or HGBΔ) in a whole blood sample." The Federal Circuit has held that words within a parathentical can serve to define the preceding phrase. *See Abbot Labs v. Novopharm Ltd*, 323 F.3d 1324, 1330 (Fed. Cir. 2003). There are similar statements in paragraphs 27 and 52 as well. It is clear from this language that "cellular" hemoglobin is equated with "intracellular hemoglobin" as contrasted with "extracellular hemoglobin." These statements make it explicitly clear that the specification defines "cellular hemoglobin" as hemoglobin that is physically located within a cell and is distinct from hemoglobin or hemoglobin substitutes that are located outside of a cell, for example in the serum or plasma. Applicant has amended herein independent claims 1, 9, 15 and 16 to particularly point out that the present invention is directed to correcting hematology measurements for the presence of "extracellular" blood substitutes. Because Chupp does not disclose methods for distinguishing cellular hemoglobin from extracellular hemoglobin, the term "hemoglobin," as used in Chupp, is clearly not the "cellular hemoglobin" of the present invention.

In summary, Applicant respectfully asserts that the Examiner has failed to establish a *prima facie* case for obviousness of independent claims 1, 9, 15 and 16 because the cited references fail to teach or suggest every limitation of the claims, either alone or in combination. Further, there is no motivation to combine Chupp, Chang, Rodriguez and Samsoondar, either in the references themselves or in the art. Having distinguished the independent claims from the

prior art, the claims dependent therefrom are also non-obvious. We do not address the dependent claims herein but reserve the right to do so. Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. § 103.

CONCLUSION

Based on the foregoing amendments and remarks, Applicant respectfully requests withdrawal of the rejection and allowance of this application.

AUTHORIZATION

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 0708-4057. A DUPLICATE OF THIS DOCUMENT IS ATTACHED.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

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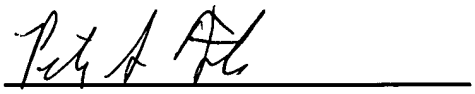
By: 

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